

## The Clinical Spectrum and Treatment of Lyme Disease

ALLEN C. STEERE, M.D., STEPHEN E. MALAWISTA, M.D.,  
NICHOLAS H. BARTENHAGEN, M.D., PHYLLIS N. SPIELER, M.D.,  
JAMES H. NEWMAN, M.D., DANIEL W. RAHN, M.D.,  
GORDON J. HUTCHINSON, M.D., JERRY GREEN, M.D.,  
DAVID R. SNYDMAN, M.D., AND ELISE TAYLOR, B.A.

*Department of Internal Medicine, Yale University School of Medicine,  
New Haven, Connecticut*

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Lyme disease was recognized as a separate entity because of close geographic clustering of affected children in Lyme, Connecticut, with what was thought to be juvenile rheumatoid arthritis. It then became apparent that Lyme disease is a complex, multisystem disorder. The illness usually begins in summer with erythema chronicum migrans and associated symptoms (stage 1). Weeks to months later, some patients develop neurologic or cardiac abnormalities (stage 2), and weeks to years later, many patients develop intermittent attacks of arthritis (stage 3), which may become chronic, with erosion of cartilage and bone. Patients with severe and prolonged illness have an increased frequency of the B-cell alloantigen, DR2. For patients with early Lyme disease, tetracycline appears to be the most effective drug, then penicillin, and finally erythromycin. High-dose intravenous penicillin is effective for the later stages of the disease.

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### RECOGNITION OF THE DISEASE

We first learned about what was to become Lyme disease in October 1975 from two mothers who reported to the Connecticut State Health Department that a number of children who lived close together in Lyme, Connecticut, were thought to have juvenile rheumatoid arthritis (JRA) [1]. To investigate these reports, physicians at the Health Department and the Yale University Rheumatology Section organized a surveillance system through contacts with the mothers, area physicians, school nurses, and local health officers in the three contiguous communities of Old Lyme, Lyme, and East Haddam (total population, 12,000). In those communities, we attempted to identify all children with inflammatory joint disease and invited them to participate in a study at the Yale University School of Medicine where a history, physical examination, and blood tests were done in an effort to determine the cause of their arthritis.

We found 39 such children. All of them had an apparently similar type of arthritis characterized by brief but recurrent attacks of asymmetric swelling and pain in a few large joints, especially the knee, over a period of years. Twelve adults, who were either parents or neighbors of affected children, were found to have a similar type of

arthritis. Although individual attacks of arthritis were often shorter than those usually seen in juvenile arthritis, it was difficult to separate the illness in Lyme residents from that entity on the basis of joint involvement alone.

However, the epidemiologic analysis of affected residents was striking. The overall prevalence rate of the disease was 4.3 per 1,000 residents; among children, it was 12.2 per 1,000, a frequency at least 100 times greater than that of JRA [2]. Even within these communities, close geographic clustering of cases was observed. Half of the affected Lyme residents lived in heavily wooded areas on two adjoining country roads, as did half of those affected in East Haddam. One in ten children living on those four roads had the illness. In addition, clustering within families was observed; six families had more than one affected member. The onset of the arthritis in the 51 patients occurred during a four-year period from July 1972 through May 1976 (the cutoff time for the initial study); the majority (55 percent) noted the onset in summer or early fall. In families with more than one affected member, those affected usually had the onset of symptoms in different years. These epidemiologic features seemed most compatible with an arthropod-transmitted illness.

Moreover, during a median of four weeks before the onset of arthritis, 13 patients (25 percent) noted an erythematous papule, thought to be an insect bite, that developed into an expanding, red annular lesion. Only two of the 159 family members of patients had such a lesion but did not develop arthritis ( $p < 0.0000001$ ). The lesion sounded most compatible with erythema chronicum migrans (ECM), described in Europe in 1909 [3]. There the lesion was associated with the bite of *Ixodes ricinus* ticks [4] and with subsequent neurologic abnormalities [5,6] but not with arthritis. Cultures and serologic tests in our patients did not suggest infection with arboviruses or any other agents known to cause arthritis. Thus, we thought that the illness in Lyme residents was a previously unrecognized clinical entity and called it "Lyme arthritis."

### CLINICAL PICTURE

During the following summer of 1976, we identified, for the first time, patients with the skin lesion, confirmed its similarity to ECM in Europe, and followed the patients prospectively [7]. Many of them subsequently developed arthritis, but some also acquired neurologic or cardiac abnormalities [8,9]. Thus, Lyme arthritis became recognized as a complex, multisystem disorder, and the name was changed to Lyme disease.

During the seven summers of 1976 through 1982, 314 patients with ECM were studied prospectively at Yale [10]. Their ages ranged from 2 to 88 years (median, 28 years), and the sex ratio was nearly one to one. Onset of the illness was generally between May 1 and November 30; the majority of onsets were in June or July [10]. The following description of the illness is based primarily on the study of these patients.

#### *Early Manifestations*

Erythema chronicum migrans, the best clinical marker for Lyme disease, usually begins as a red macule or papule [7,10]. Approximately 30 percent of the patients remember a tick bite at the site of the lesion within 3 to 32 days before it forms there. As the area of redness around the center expands, most lesions continue to have bright red outer borders and partial central clearing (PLATE 1). However, in some patients, ECM is less characteristic. The centers of early lesions sometimes become intensely erythematous and indurated, as in streptococcal cellulitis; or the center becomes vesicular and necrotic, as in tularemia. In some instances, migrating lesions

remain an even intense red, several red rings are found within the outside one, or the central area turns blue before it clears. Although the lesion can be located anywhere, the thigh, groin, and axilla are particularly common sites. The lesion is hot to touch, but often not painful. Histologically, the center of ECM shows dermal and epidermal changes, but only dermal changes in the periphery (Fig. 1), findings suggestive of an arthropod bite.

In some patients, the disease remains localized to a single skin lesion accompanied by minor constitutional symptoms—malaise and fatigue, headache, fever and chills, and regional lymphadenopathy. The illness in these patients seems very similar to ECM as described in Europe [3,4]. However, unlike the European experience, the disease here often seems to disseminate [10]. Within several days after onset of the initial skin lesion (ECM), many patients develop multiple annular secondary lesions (PLATE II). Although their appearance is similar to initial lesions, they are generally smaller, migrate less, and lack indurated centers; they are not associated with previous tick bites. Patients with secondary lesions may be thought to have erythema multiforme; however, in Lyme disease we have not seen blistering, mucosal lesions, or involvement of the palms and soles. During this period, some patients develop other dermatologic findings including malar rash, conjunctivitis, urticaria, or small evanescent red blotches and circles.

Patients with disseminated disease sometimes have evidence of meningeal irritation, mild encephalopathy, migratory musculoskeletal pain, hepatitis, generalized lymphadenopathy or splenomegaly, sore throat, non-productive cough, or testicular swelling [10]. Except for lethargy and fatigue, which are often constant and may be incapacitating, the early signs and symptoms are typically intermittent and changing. For example, a patient might experience predominantly headache and stiff neck for several days. After a few days of improvement, musculoskeletal pain might begin.

During this stage, the commonest non-specific laboratory abnormalities are a high erythrocyte sedimentation rate (53 percent of patients), an elevated total serum IgM level (33 percent), or an increased serum glutamic oxaloacetic transaminase (SGOT) level (19 percent) [10]. The latter finding supports the clinical impression that mild hepatitis may be a feature of early Lyme disease. A few patients have microscopic hematuria, sometimes with mild proteinuria (dipstick), which has been the only evidence of renal involvement. Regardless of treatment, the signs and symptoms of

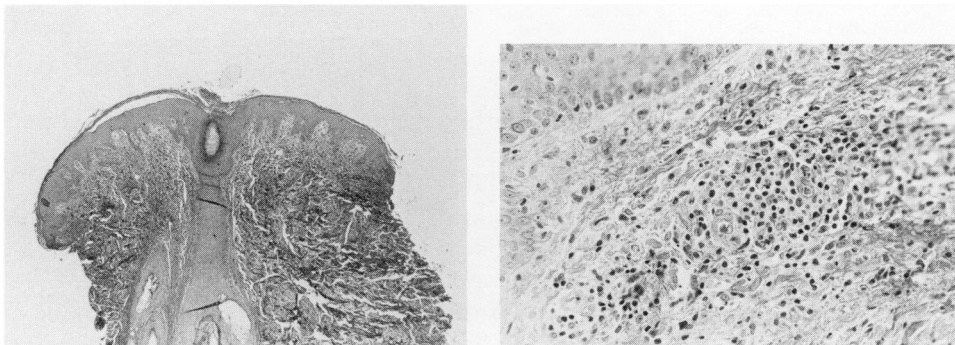


FIG. 1. Histology of an initial skin lesion. *Left:* There is an infiltration of mononuclear cells throughout all layers of the dermis. *Right:* At higher power, the cellular infiltrate is seen to consist primarily of lymphocytes, histocytes, and a few plasma and mast cells.

stage one usually fade within three to four weeks (range, 1 day to 14 months). However, the dermatologic manifestations of the illness sometimes recur.

### *Later Manifestations*

**Nervous System** Symptoms suggestive of meningeal irritation sometimes occur at the beginning of the illness when ECM is present [10]. Such individuals often have episodic attacks of excruciating headache and neck pain, stiffness, or pressure typically lasting hours. During the first one or two weeks of illness, such symptoms are not associated with a spinal fluid pleocytosis or objective neurologic deficit. However, after several weeks to months, about 15 percent of patients develop frank neurologic abnormalities. The usual triad of symptoms consists of meningitis, cranial neuropathy (particularly Bell's palsy), and peripheral radiculoneuropathy. However, any of these manifestations may occur alone [8]. In untreated patients, neurologic abnormalities typically last for months but usually resolve completely.

**Heart** Within several weeks after the onset of illness, about 8 percent of patients develop cardiac involvement [9]. The commonest abnormality is fluctuating degrees of atrioventricular block (first degree, Wenckebach, or complete heart block). Some patients have evidence of more diffuse cardiac involvement including electrocardiographic changes compatible with acute myopericarditis, radionuclide evidence of mild left ventricular dysfunction or, rarely, cardiomegaly. The duration of cardiac involvement is usually brief (three days to six weeks) and rarely recurs. The clinical picture in these patients has similarities to acute rheumatic fever, but in Lyme disease, complete heart block may be more common, myopericardial involvement tends to be milder, and valves seem not to be affected.

**Joints** Within a few weeks to two years after the onset of illness, about 60 percent of patients develop arthritis [7,11,12]. If joint involvement occurs early in the illness, the typical pattern is one of migratory musculoskeletal pain in joints, tendons, bursae, muscle, or bone, often without joint swelling. The pain tends to affect only one or two sites at a time and usually lasts a few hours to several days in a given location. Frank arthritis with marked joint swelling usually does not begin until months after the onset of the illness. At that time, patients often experience intermittent attacks of joint swelling and pain, primarily in large joints, especially the knee, usually one or two joints at a time. Affected knees are commonly much more swollen than painful, often hot, rarely red; Baker's cysts sometimes form and rupture early. However, both large and small joints may be affected and a few patients have had symmetrical polyarthritis, as in rheumatoid arthritis. Attacks of arthritis, which generally last from a few weeks to months, typically recur for several years. Late in the illness, fatigue is common with active joint involvement, but fever or other systemic symptoms are unusual. Joint fluid white cell counts vary from 500 to 110,000 cells/mm<sup>3</sup> with mostly polymorphonuclear leukocytes [7]. Total protein ranges from 3 to 8 g/dl. C3 and C4 levels are generally greater than one-third and glucose levels usually greater than two-thirds of that of serum.

In about 10 percent of patients with arthritis, involvement in large joints becomes chronic, with erosion of cartilage and bone [11,12]. Synovial biopsies show surface deposits of fibrin, villous hypertrophy, vascular proliferation, and a heavy infiltration of mononuclear cells, including plasma cells presumably capable of producing antibody locally (Fig. 2) [7,11,12]. In one patient with chronic Lyme arthritis, synovium grown in tissue culture produced large amounts of collagenase and prostaglandin E<sub>2</sub> [12]. Thus, in Lyme disease, the joint fluid cell counts, the immune reactants (except for rheumatoid factor), the synovial histology, the amounts of

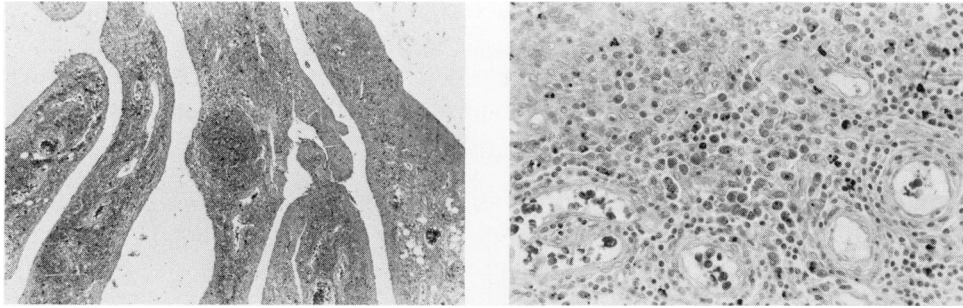


FIG. 2. Histology of affected synovium. *Left:* Individual polypoid stalks show central edema, congestion, vascular proliferation, and a heavy infiltration of mononuclear cells. *Right:* At higher power, the cellular infiltrate is shown to consist primarily of small lymphocytes and plasma cells.

synovial enzymes released, and the resulting destruction of cartilage and bone may be similar to that in rheumatoid arthritis.

#### *Variations in Clinical Manifestations*

We have come to think of Lyme disease as an illness that occurs in stages, with remissions and exacerbations and different clinical manifestations at each stage (Table 1). The disorder usually begins with ECM and associated symptoms (stage 1). Weeks to months later, some patients develop neurologic or cardiac abnormalities (stage 2), and weeks to years later, many patients develop arthritis (stage 3). However, it should be emphasized that marked variation is possible in the clinical expression of the disease. Even without treatment, some patients have very mild disease (e.g., ECM alone with no other manifestations). At the opposite end of the spectrum, an occasional patient will have severe involvement of skin, nerves, heart, and joints at the same time. Incomplete disease pictures are also possible. Some patients lack ECM but have other non-specific symptoms associated with stage one. These patients are often thought to have viral infections. In other patients, stage one is asymptomatic and the presenting signs of the disease are neurologic or joint involvement. These patients may be diagnosed as having aseptic meningitis, rheumatoid arthritis, juvenile arthritis, or Reiter's syndrome.

The development of severe and prolonged illness is associated with a particular genetic susceptibility [11,13]. In a study of 45 patients at the two ends of the clinical spectrum of Lyme disease, those with severe and prolonged illness (ECM followed by meningitis or chronic arthritis) had an increased frequency of the B-cell alloantigen, DR2 (67 percent of patients) compared to 36 percent of those with mild and brief illness (ECM alone) (odds ratio = 3.4,  $p < 0.05$ ) or to 25 percent of those in a

TABLE 1  
Stages of Lyme Disease\*

Stage	Manifestation
1	ECM and associated symptoms
2	Neurologic or cardiac abnormalities
3	Arthritis

\*The stages may overlap or occur alone.

normal population (odds ratio = 6,  $p < 0.0001$ ). Thus, Lyme disease seems to fit within a pathogenetic framework thought to be important in several rheumatic diseases; namely, in genetically susceptible individuals, certain infectious agents may be associated with a characteristic immune response that leads to arthritis.

### TREATMENT

We initially suspected that Lyme disease was a viral illness. However, in Europe, where associated arthritis was unknown, ECM was said to respond to antibiotic therapy [14,15], and case reports supporting that conclusion had also appeared in the United States [16,17]. Therefore, during the 1977 and 1979 summers, we gave antibiotics to patients with active ECM and compared the results with those in untreated patients from the summers of 1976 and 1978. Based on these observations, we reported that penicillin, given early in the illness, shortened the duration of ECM and appeared to prevent or attenuate subsequent arthritis [18].

To further clarify these findings, during 1980 and 1981, 108 patients with early Lyme disease were assigned treatment randomly with phenoxymethyl penicillin, erythromycin, or tetracycline, in each instance 250 mg four times a day for ten days [19]. The patients in each group had similar age and sex distributions, and the mean duration in each from the onset of illness to the beginning of antibiotic therapy was nine to ten days. Fourteen percent of patients, generally those with more severe disease, had an intensification of symptoms during the first 24 hours after the start of therapy. This Jarisch-Herxheimer-like reaction occurred more often with penicillin and tetracycline than with erythromycin, presumably because of faster killing of larger numbers of organisms.

ECM and its associated symptoms resolved significantly faster in penicillin- or tetracycline-treated patients than in those given erythromycin (mean duration, 5.4 and 5.7 versus 9.2 days,  $F = 3.38$ ,  $p < 0.05$ ) [19]. In addition, fewer patients given penicillin (5 percent) or tetracycline (8 percent) than those treated with erythromycin (17 percent) required retreatment (ten more days of antibiotics) because of persistence of symptoms or immediate relapse. More important, none of the 39 patients given tetracycline developed major late complications (myocarditis, meningoencephalitis, or recurrent attacks of arthritis) compared with 3 of 40 penicillin-treated patients (8 percent) and 4 of 29 given erythromycin (14 percent) ( $p = 0.07$ ). In 1982, all 49 adult patients were given tetracycline; again, none of them developed major complications. Thus, for adults early in the illness, tetracycline, 250 mg four times a day, seems to be the drug of choice, followed by phenoxymethyl penicillin, 500 mg four times a day, and erythromycin, 250 mg four times a day, in each instance for at least ten days or for up to 20 days if symptoms persist or recur [19]. In children, we recommend phenoxymethyl penicillin 50 mg/kg/d (not less than 1 g/d or more than 2 g/d) in divided doses for the same duration or, in cases of penicillin allergy, erythromycin, 30 mg/kg/d, in divided doses for 15 or 20 days.

Regardless of the antibiotic agent given, nearly half of patients still experienced minor late complications—recurrent episodes of headache or pain in joints, tendons, bursae, or muscles, often accompanied by lethargy [19]. Their physical examinations were usually normal. Symptoms were often reminiscent of those experienced at the beginning of the illness, but were generally briefer and less severe. They correlated significantly with the initial severity of the illness. In a given attack, pain usually occurred in one or two sites and lasted from hours to days. With frequent attacks, the pain was often migratory. Such attacks sometimes recurred for several years. The pathogenesis of these symptoms is unknown. A severely depleted

number of live spirochetes may continue to produce these less serious but sometimes debilitating symptoms. Alternately, they may not require the persistence of an intact spirochete.

Can the later manifestations of Lyme disease be treated with antibiotic therapy? In 1981 and 1982, we treated 12 patients with intravenous penicillin, 20 million U a day in divided doses, for neurologic abnormalities of Lyme disease [20]. Headache, stiff neck, and radicular pain usually began to subside by the second day of therapy and were often gone by seven to ten days. Compared to 15 previous patients treated with prednisone alone, the duration of meningitic symptoms was significantly shorter in those given penicillin (mean duration, one versus 29 weeks,  $p < 0.000001$ ). However, in both groups a mean of seven to eight weeks was required for complete recovery of motor deficits. Thus, we concluded that high-dose intravenous penicillin is effective therapy for neurologic abnormalities of Lyme disease. However, similar to the experience with oral antibiotics for ECM, 3 of the 12 patients continued to have frequent arthralgias, musculoskeletal pain, and fatigue despite penicillin therapy.

Cardiac involvement should also be treated with antibiotics, either oral tetracycline or intravenous penicillin [unpublished observations]. In addition, our practice is to include aspirin therapy, generally 3.6 g/d, or prednisone, 40 to 60 mg/d, if the patient has complete heart block and cardiomegaly [9].

Established Lyme arthritis can also be treated successfully with high-dose intravenous penicillin [21]. In a double-blind, placebo-controlled trial, seven of 16 patients who received intramuscular benzathine penicillin remained well afterward, but all 20 patients given saline continued to have attacks of arthritis ( $p = 0.001$ ). In a subsequent study, 13 of 20 patients given penicillin G, 20 million U a day intravenously for ten days, have remained well, including both patients who were Bicillin failures.

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**PLATE I.** Erythema chronicum migrans. A ten-day-old lesion has gradually expanded to 10 cm and is beginning to have a brighter red border.



**PLATE II.** Multiple annular secondary lesions. Four days after onset of ECM, small secondary lesions have appeared on the trunk and legs.